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Chemical:	**Oxamyl**
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Memo Date:	**02/03/2000**
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

FEB 3 2000

013974

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Oxamyl: Review of Cholinesterase Inhibition Reversibility of Carbamates in Rats (MRID 44472001)

PC Nos.: 103801
Tox. Chem. No.: 1561A
Project No.: D248550
Submission No.: S547450

To: Betty Shackleford/Carmelita White
Project Manager 53
Reregistration Branch III
Special Review and Reregistration Division (7508W)

From: Guruva B. Reddy
Reregistration Review Branch II
Health Effects Division (7509C)
2/3/2000

Thru: Robert Fricke 3 Feb 2000
Reregistration Review Branch II
Health Effects Division (7509C)

I. CONCLUSIONS:

Reregistration Review Branch II reviewed the reversibility study with carbamates insecticides in rats (MRID 44472001) and the study is classified **Acceptable/Non-Guideline** since the study was not intended to fulfill the guideline requirements. A copy of the DER is enclosed.

Copy of the DER enclosed.

II. ACTION REQUESTED

The DuPonte de Nemours and Company submitted cholinesterase inhibition reversibility study with carbamate insecticides in rats (MRID 44472001). The objective of the study was to determine the times frames of cholinesterase inhibition between oxamyl and methomyl. The study was submitted in support of preregistration of oxamyl for terrestrial food use on field crops, vegetables, fruits and ornamentals.

III. STUDIES REVIEWED

STUDY/CLASSIFICATION	RRB2 COMMENTS
Non-Guideline Cholinesterase inhibition reversibility study with carbamate insecticides Species: rat Haskell Laboratory for Toxicology and Industrial Medicine Lab. Project ID: HL-1997-00641; November 10, 1997. MRID 44472001. **Acceptable**	In a cholinesterase inhibition reversibility study (MRID 44472001), oxamyl (98.3% a.i.) or methomyl (98.6% a.i.) technical were administered by gavage to Crl:CD®BR rats (40/sex/group) at levels of 0 or 1 mg/kg (oxamyl technical) or 0 or 3 mg/kg (methomyl technical). Ten rats/sex/group were sacrificed at 0.5, 2, 3, and 4 hours postdosing and RBC, plasma, and brain cholinesterase activities were determined. This study was performed to determine the length of time needed for recovery from inhibition of cholinesterase activity. There was no mortality in treated or control groups. Tremors were observed ($p<0.05$) at 0.5 hours postdosing in 74/80 animals treated with oxamyl technical and 23/80 animals treated with methomyl technical vs. 0/160 controls. There were no clinical signs at 2 hours postdosing or beyond. Red blood cell (RBC) cholinesterase activity was decreased ($p<0.05$) compared with concurrent controls in male and female (↓58-61%) rats dosed with oxamyl technical at 0.5 hours postdosing; the activity returned to normal levels by 2 hours postdosing. RBC cholinesterase activity was decreased ($p<0.05$) in male and female (↓41-56%) rats dosed with methomyl technical at 0.5 hours postdosing and in male rats at 2 hours postdosing (↓24%); the activity returned to normal levels in male rats by 3 hours postdosing and in females rats by 2 hours postdosing. Plasma cholinesterase activity was decreased ($p<0.05$) in male and female (↓50-57%) rats dosed with oxamyl technical at 0.5 hours postdosing; the activity returned to normal levels by 2 hours postdosing. Plasma cholinesterase activity was decreased ($p<0.05$) in male rats at 0.5 (↓27%) and 2 (↓19%) hours postdosing with methomyl technical and returned to normal levels by 3 hours postdosing. Plasma cholinesterase activity was not significantly inhibited in female rats at any timepoint. Brain cholinesterase activity was decreased ($p<0.05$) in male and female rats at 0.5 hours (↓45-48%) and in female rats at 2 hours (↓11%) postdosing with oxamyl technical; the activity returned to normal levels by 2 hours postdosing in males and 3 hours postdosing in females. Brain cholinesterase activity was decreased ($p<0.05$) in male and female rats at 0.5 hours (↓39-46%) and in male rats at 2 hours (↓16%) postdosing with methomyl technical; the activity returned to normal levels by 3 hours postdosing in males and 2 hours postdosing in females. In summary, oxamyl technical and methomyl technical caused tremors within 30 minutes postdosing with recovery occurring within 2 hours postdosing for both test articles. Oxamyl technical at 1 mg/kg produced inhibition of plasma, RBC, and brain cholinesterase activities 30 minutes after treatment in male and female rats with complete recovery by 2 hours after treatment, except for female brain cholinesterase activity, which returned to normal levels by 3 hours postdosing. Methomyl technical at 3 mg/kg produced inhibition of plasma, RBC, and brain cholinesterase activities in male rats and RBC and brain cholinesterase in females rats 30 minutes after treatment with complete recovery at the 2-hour and 3-hour sampling times in females and males, respectively. No inhibition of plasma cholinesterase activity was observed in female rats at any timepoint. Minimal residual inhibition of blood and brain cholinesterase activities was apparent in males 2 hours after treatment. This cholinesterase inhibition reversibility study is classified **acceptable (nonguideline)** as it is not a required guideline study. It is acceptable for the purpose for which it was intended.

DATA EVALUATION RECORD 013974

OXAMYL and METHOMYL TECHNICAL

Study Type: Non-Guideline; Reversibility Study with Carbamate Insecticides in Rats

Work Assignment No. 1-01-46 (MRID 44472001)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Guy R. Beretich, Ph.D.
Signature: Guy Beretich
Date: 8/30/99

Secondary Reviewer
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 9/1/99

Program Manager
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 9/7/99

Quality Assurance:
Steven Brecher, Ph.D.
Signature: Steven Brecher
Date: 9/7/99

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Guruva Reddy, DVM, PhD
Reregistration Branch 2/HED (7509C)

Work Assignment Manager: Sanjivani Diwan, Ph.D.
Toxicology Branch 1/HED (7509C)

GReddy 9/21/99

Sanjivani Diwan 9/21

DATA EVALUATION RECORD

013974

STUDY TYPE: Cholinesterase Inhibition Reversibility - Rat
OPPTS Number: N/A

OPP Guideline Number: N/A

DP BARCODE: D248550
P.C. CODE: 103801 Oxamyl; 090301 Methomyl

SUBMISSION CODE: S547450
TOX. CHEM. NOs.:
Oxamyl - 561A
Methomyl - 549C

TEST MATERIAL (PURITY): Oxamyl (98.3% a.i.) and methomyl (98.6% a.i.) technical

SYNONYMS: Oxamyl: methyl 2-(dimethylamino)-N-[[(methylamino)carbonyl]oxy]-2-oxo-ethanimidothioate; methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]-1-thiooxamimidate; ethanimidothioic acid, 2-(dimethylamino)-N-[[(methylamino)carbonyl]oxy]-2-oxo-, methyl ester.

Methomyl: S-methyl N-[(methylcarbamoyl)oxy]thioacetimidate; ethanimidothioic acid, N-[[(methylamino)carbonyl]oxy]-, methyl ester.

CITATION: Malley, L.A. (1997) Reversibility Study with Carbamate Insecticides in Rats. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware. Laboratory Project ID: HL-1997-00641. November 10, 1997. MRID 44472001. Unpublished.

SPONSOR: Agricultural Products, E.I. du Pont de Nemours and Company, Barley Mill Plaza, Wilmington, Delaware.

EXECUTIVE SUMMARY: In a cholinesterase inhibition reversibility study (MRID 44472001), oxamyl (98.3% a.i.) or methomyl (98.6% a.i.) technical were administered by gavage to Crl:CD®BR rats (40/sex/group) at levels of 0 or 1 mg/kg (oxamyl technical) or 0 or 3 mg/kg (methomyl technical). Ten rats/sex/group were sacrificed at 0.5, 2, 3, and 4 hours postdosing and RBC, plasma, and brain cholinesterase activities were determined. This study was performed to determine the length of time needed for recovery from inhibition of cholinesterase activity.

There was no mortality in treated or control groups. Tremors were observed ($p<0.05$) at 0.5

hours postdosing in 74/80 animals treated with oxamyl technical and 23/80 animals treated with methomyl technical vs. 0/160 controls. There were no clinical signs at 2 hours postdosing or beyond.

Red blood cell (RBC) cholinesterase activity was decreased ($p<0.05$) compared with concurrent controls in male and female (↓58-61%) rats dosed with oxamyl technical at 0.5 hours postdosing; the activity returned to normal levels by 2 hours postdosing. RBC cholinesterase activity was decreased ($p<0.05$) in male and female (↓41-56%) rats dosed with methomyl technical at 0.5 hours postdosing and in male rats at 2 hours postdosing (↓24%); the activity returned to normal levels in male rats by 3 hours postdosing and in females rats by 2 hours postdosing.

Plasma cholinesterase activity was decreased ($p<0.05$) in male and female (↓50-57%) rats dosed with oxamyl technical at 0.5 hours postdosing; the activity returned to normal levels by 2 hours postdosing. Plasma cholinesterase activity was decreased ($p<0.05$) in male rats at 0.5 (↓27%) and 2 (↓19%) hours postdosing with methomyl technical and returned to normal levels by 3 hours postdosing. Plasma cholinesterase activity was not significantly inhibited in female rats at any timepoint.

Brain cholinesterase activity was decreased ($p<0.05$) in male and female rats at 0.5 hours (↓45-48%) and in female rats at 2 hours (↓11%) postdosing with oxamyl technical; the activity returned to normal levels by 2 hours postdosing in males and 3 hours postdosing in females. Brain cholinesterase activity was decreased ($p<0.05$) in male and female rats at 0.5 hours (↓39-46%) and in male rats at 2 hours (↓16%) postdosing with methomyl technical; the activity returned to normal levels by 3 hours postdosing in males and 2 hours postdosing in females.

In summary, oxamyl technical and methomyl technical caused tremors within 30 minutes postdosing with recovery occurring within 2 hours postdosing for both test articles. Oxamyl technical at 1 mg/kg produced inhibition of plasma, RBC, and brain cholinesterase activities 30 minutes after treatment in male and female rats with complete recovery by 2 hours after treatment, except for female brain cholinesterase activity, which returned to normal levels by 3 hours postdosing. Methomyl technical at 3 mg/kg produced inhibition of plasma, RBC, and brain cholinesterase activities in male rats and RBC and brain cholinesterase in females rats 30 minutes after treatment with complete recovery at the 2-hour and 3-hour sampling times in females and males, respectively. No inhibition of plasma cholinesterase activity was observed in female rats at any timepoint. Minimal residual inhibition of blood and brain cholinesterase activities was apparent in males 2 hours after treatment.

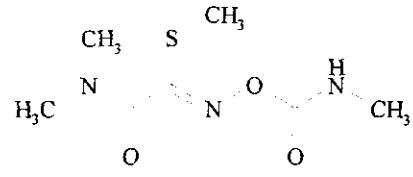
This cholinesterase inhibition reversibility study is classified **acceptable (nonguideline)** as it is not a required guideline study. It is acceptable for the purpose for which it was intended.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, and Quality Assurance Statements were provided.

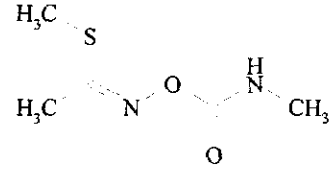
I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Oxamyl technical; methomyl technical
   Description: Oxamyl technical - off-white solid; methomyl technical - white solid
   Lot/Batch #: Oxamyl technical - DPX-D1410-196; methomyl technical - DPX-X1179-512
   Purity: Oxamyl technical - 98.3% a.i.; methomyl technical - 98.6% a.i.
   Storage: Not specified.
   CAS #: Oxamyl -23135-22-0; methomyl - 16752-77-5
   Structure: Oxamyl Technical



   Structure: Methomyl Technical



2. Vehicle: Deionized water

3. Test animals: Species: Rat
   Strain: Crl:CD®BR
   Age and weight at study initiation: Approx. 48-49 days old; 101.1-146.1 g (males) and 72.1-109.5 g (females) day after arrival.
   Source: Charles River Laboratories, Inc.
   Housing: Individually in stainless steel hanging wire-mesh cages
   Diet: Purina® Certified Rodent Chow® #5002, ad libitum
   Water: United Water Delaware, ad libitum
   Environmental conditions:
      Temperature: Approximately 23±1 °C
      Humidity: Approximately 50±10%
      Air changes: Not reported
      Photoperiod: 12 h dark/12 h light
   Acclimation period: 13-14 days

B. STUDY DESIGN:

1. In life dates - start: 6/9/97 end: 6/17/97

2. Animal assignment: Animals were assigned by a body weight-dependent, computer-generated randomization procedure to treatment groups as indicated in Table 1.

Table 1. Study design

Sacrifice Timepoints (hours postdosing)	Oxamyl Technical		Methomyl Technical	
	Dose (mg/kg)			
	0	1	0	3
	Number of Animals/Sex			
0.5	10	10	10	10
2	10	10	10	10
3	10	10	10	10
4	10	10	10	10

3. Dose selection: Dosages were selected based on the results of a previous acute oral neurotoxicity study (DuPont Haskell Laboratory Report No. HLR-1118-96) and pilot acute oral toxicity studies (no citations provided). In these studies, dose levels effective in inhibiting cholinesterase activities, time-to-peak effect, and time to recovery were determined. For oxamyl technical, an acute oral neurotoxicity study demonstrated that ≥0.75 mg/kg in females and ≥1.0 mg/kg in males was able to produce inhibition of cholinesterase activity. A subsequent pilot study demonstrated that the time-to-peak inhibition of plasma and RBC cholinesterase activities (↓57-70%) was 0.5 hours postdosing and recovery was complete by 3 hours postdosing. Clinical signs of cholinesterase inhibition followed a similar course. For methomyl technical, an initial pilot study at doses of 1, 3, 5, 6, 10, or 15 mg/kg to 5 rats/sex/dose demonstrated that clinical signs of cholinesterase inhibition occurred at ≥5 mg/kg. A subsequent time-to-peak effect study at doses of 0, 3, 6, and/or 15 mg/kg demonstrated that plasma and RBC cholinesterase activities were inhibited 43-62% at ≥3 mg/kg and the time-to-peak effect was 0.5 hours postdosing. In a final time-to-recovery study conducted on males rats at doses of 0, 3, or 6 mg/kg the plasma and RBC cholinesterase activities were inhibited 32-64% at 0.5 hours postdosing and 11-17% (plasma) and 0-28% (RBC) at 2 hours postdosing. No inhibition was apparent at 4 hours postdosing, indicating that recovery was complete.

Based upon the results of these studies, the doses summarized in Table 1 were selected for the reversibility study. In addition, the sampling times of 0.5, 2, 3, and 4 hours postdosing were selected.

4. Gavage formulation preparation and analysis: Gavage formulations were prepared on the morning of dosing. Dilutions were adjusted for purity. One sample of the vehicle (deionized water) and each test solution (10 mLs) was collected on the day of dosing and analyzed for concentration.

   Results: Concentration analyses (range as % of nominal): oxamyl technical - 95.9-98.2%; methomyl technical - 95.0-97.3%.

   The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

5. Statistics: Clinical signs were evaluated with Fisher's Exact Test. Cholinesterase activity data were analyzed by a one-way analysis of variance and pair-wise comparisons made with Dunnett's test. Homogeneity of variances was performed with Levene's test and normality tested with the Shapiro-Wilk test. If the Shapiro-Wilk test was significant, nonparametric comparisons were applied (Kruskal-Wallis test and Dunn's Multiple Comparisons). If the Shapiro-Wilk test was not significant, but Levene's test was significant, a robust version of Dunnett's test was used.

C. METHODS:

1. Observations: Animals were inspected for clinical signs prior to dosing, at approximately 0.5 hours postdosing, and at the time of sacrifice (0.5, 2, 3, or 4 hours).

2. Body weight and body weight gains: Weights were recorded immediately before dosing in order to calculate the dosage for each rat.

3. Cholinesterase activities: Blood was collected from 10 animals/sex/group at 0.5, 2, 3, or 4 hours postdosing for plasma and RBC cholinesterase activities determination. Animals were subjected to light carbon dioxide anesthesia and blood was collected from the orbital sinus. Animals were then sacrificed by carbon dioxide asphyxiation and the brains removed for brain cholinesterase activity determination. Blood samples were maintained on ice; plasma and RBC cholinesterase activities were determined on the day of collection, whereas brain tissue was frozen at minus 70°C and analyzed at a later date.

II. RESULTS

A. Observations

1. Toxicity -
   Oxamyl technical: Tremors were noted in 38/40 males and 36/40 females vs. 0/80 controls ($p<0.05$) at 0.5 hours postdosing. One treated male exhibited a wet chin, indicative of salivation, at 0.5 hours postdosing. There were no clinical signs at 2 hours postdosing.

   Methomyl technical: Tremors were noted in 17/40 males and 6/40 females vs. 0/80 controls ($p<0.05$) at 0.5 hours postdosing. One treated male exhibited a clear ocular discharge from both eyes and one control male exhibited a red face stain at 0.5 hours postdosing. There were no clinical signs at 2 hours postdosing.

2. Mortality - There was no mortality in either treatment group or controls.

B. Body weights - Body weights were not reported.

C. Cholinesterase activities

1. RBC cholinesterase activity
   Oxamyl technical - RBC cholinesterase activity (Table 2) was decreased ($p<0.05$) compared with concurrent controls in male (↓58%) and female (↓61%) rats at 0.5 hours postdosing and returned to normal levels by 2 hours postdosing.

   Methomyl technical - RBC cholinesterase activity was decreased ($p<0.05$) in male (↓56) and female (↓41%) rats at 0.5 hours postdosing and in male rats at 2 hours postdosing (↓24%) and returned to normal levels in male rats by 3 hours postdosing and in females rats by 2 hours postdosing.

Table 2. Red blood cell cholinesterase activity (U/L) in male and female rats treated once by gavage with oxamyl technical or methomyl technical.[a]

Hours postdosing	Oxamyl Technical				Methomyl Technical			
	Male		Female		Male		Female	
	Control	1 mg/kg	Control	1 mg/kg	Control	3 mg/kg	Control	3 mg/kg
0.5	1760	**740*(↓58)**	2176	**856*(↓61)**	2074	**920*(↓56)**	2342	**1374*(↓41)**
2	1748	1782	1994	1870	2294	**1754*(↓24)**	2062	2084
3	1912	2148	1796	1884	2042	1990	2250	2146
4	2456	2132	1858	2006	2126	2082	2334	2430

a Data extracted from the study report, Tables 6 through 9, pages 32 through 35.
* Significantly different from controls at $p<0.05$. Percent change from controls is presented parenthetically.

2. Plasma cholinesterase activity

Oxamyl technical - Plasma cholinesterase activity (Table 3) was decreased ($p<0.05$) compared with concurrent controls in male (↓57%) and female (↓50%) rats at 0.5 hours postdosing and returned to normal levels by 2 hours postdosing.

Methomyl technical - Plasma cholinesterase activity was decreased ($p<0.05$) in male rats at 0.5 (↓27%), 2 (↓19%), and 4 (↓13%) hours postdosing, but not at 3 hours postdosing. Plasma cholinesterase activity was not significantly inhibited in female rats at any timepoint.

Table 3. Plasma cholinesterase activity (U/L) in male and female rats treated once by gavage with oxamyl technical or methomyl technical.[a]

Hours postdosing	Oxamyl Technical				Methomyl Technical			
	Male		Female		Male		Female	
	Control	1 mg/kg	Control	1 mg/kg	Control	3 mg/kg	Control	3 mg/kg
0.5	477	205*(↓57)	814	404*(↓50)	421	306*(↓27)	784	703
2	493	447	782	732	437	356*(↓19)	835	782
3	438	451	783	726	449	449	857	884
4	443	447	743	793	458	399*(↓13)	856	738

a Data extracted from the study report, Tables 6 through 9, pages 32 through 35.
* Significantly different from controls at $p<0.05$. Percent change from controls is presented parenthetically.

3. Brain cholinesterase activity

Oxamyl technical - Brain cholinesterase activity (Table 4) was decreased ($p<0.05$) compared with concurrent controls in male rats at 0.5 hours (↓45%) and 2 hours (↓4%) postdosing and in female rats at 0.5 hours (↓48%) and 2 hours (↓11%) postdosing. There was a significant increase ($p<0.05$) in the cholinesterase activity in males at 4 hours (↑5%). The differences at 2 and 4 hours in males were minor and/or an increase and therefore considered not to be of toxicological concern. Therefore, brain cholinesterase activity returned to normal levels by 2 hours postdosing in males and 3 hours postdosing in females.

Methomyl technical - Brain cholinesterase activity was decreased ($p<0.05$) in male rats at 0.5 hours (↓46%), 2 hours (↓16%), and 3 hours (↓8%) postdosing and in female rats at 0.5 hours (↓39%), 2 hours (↓8%), and 3 hours (↓8) postdosing. The differences at 2 hours in females and 3 hours in males and females were minor and considered not to be of toxicological concern. Therefore, brain cholinesterase activity returned to normal levels by 3 hours postdosing in males and 2 hours postdosing in females.

Table 4. Brain cholinesterase activity (U/L) in male and female rats treated once by gavage with oxamyl technical or methomyl technical.[a]

Hours postdosing	Oxamyl Technical				Methomyl Technical			
	Male		Female		Male		Female	
	Control	1 mg/kg	Control	1 mg/kg	Control	3 mg/kg	Control	3 mg/kg
0.5	11.25	6.22*(↓45)	12.15	6.26*(↓48)	12.30	6.65*(↓46)	12.12	7.37*(↓39)
2	11.62	11.12*(↓4)	11.84	10.51*(↓11)	11.98	10.06*(↓16)	12.11	11.17*(↓8)
3	12.23	12.10	12.26	11.95	11.96	11.06*(↓8)	12.46	11.43*(↓8)
4	11.58	12.12*(↑5)	12.58	12.55	11.83	11.76	12.09	12.07

a Data extracted from the study report, Tables 6 through 9, pages 32 through 35. Percent change from controls is presented parenthetically.

* Significantly different from controls at $p<0.05$.

III. DISCUSSION

A. Investigator's conclusions - Oxamyl technical and methomyl technical caused clinical signs indicative of cholinesterase activity inhibition within 30 minutes postdosing. Recovery occurred within 2 hours postdosing for both test articles.

Oxamyl technical at 1 mg/kg produced inhibition of plasma, RBC, and brain cholinesterase activities 30 minutes after treatment in male and female rats. Recovery was complete by 2 hours after treatment.

Methomyl technical at 3 mg/kg produced inhibition of plasma, RBC, and brain cholinesterase activities 30 minutes after treatment in male and female rats. In males, only minimal residual inhibition of blood and brain cholinesterase activities was apparent 2 hours after treatment. Recovery was complete at the 2-hour and 3-hour sampling times in females and males, respectively.

B. Reviewer's discussion - Male and female Crl:CD®BR rats (40/sex/group in 2 treated groups and 40/sex/group in 2 control groups) were gavaged with oxamyl technical at 1 mg/kg or methomyl technical at 3 mg/kg. Ten animals/sex/group were sacrificed at 0.5, 2, 3, or 4 hours postdosing and RBC, plasma, and brain cholinesterase activities determined. Formulation analyses confirmed that nominal formulation concentrations were achieved.

There was no mortality in treated or control groups. Tremors were observed in 38/40 males and 36/40 females vs. 0/80 controls ($p<0.05$) at 0.5 hours postdosing in animals treated with oxamyl technical. There were no clinical signs at 2 hours postdosing or beyond. Tremors

were observed in 17/40 males and 6/40 females vs. 0/80 controls ($p<0.05$) at 0.5 hours postdosing in animals treated with methomyl technical. There were no clinical signs at 2 hours postdosing or beyond.

RBC cholinesterase activity was decreased ($p<0.05$) in male (↓58%) and female (↓61%) rats dosed with oxamyl technical at 0.5 hours postdosing; activity returned to normal levels by 2 hours postdosing. RBC cholinesterase activity was decreased ($p<0.05$) in male (↓56) and female (↓41%) rats dosed with methomyl technical at 0.5 hours postdosing and in male rats at 2 hours postdosing (↓24%) with activity returning to normal by 3 hours postdosing and in females rats by 2 hours postdosing.

Plasma cholinesterase activity was decreased ($p<0.05$) in male (↓57%) and female (↓50%) rats dosed with oxamyl technical at 0.5 hours postdosing with activity returning to normal levels by 2 hours postdosing. Plasma cholinesterase activity was decreased ($p<0.05$) in male rats at 0.5 (↓27%), 2 (↓19%), and 4 (↓13%) hours postdosing with methomyl technical, but not at 3 hours postdosing. Because there was no difference at 3 hours postdosing, the decrease at 4 hours was not considered treatment-related. Therefore, plasma cholinesterase activity returned to normal levels in males by 3 hours postdosing. Plasma cholinesterase activity was not significantly inhibited in female rats at any timepoint.

Brain cholinesterase activity was decreased ($p<0.05$) in male rats at 0.5 hours (↓45%) and 2 hours (↓4%) postdosing and in female rats at 0.5 hours (↓48%) and 2 hours (↓11%) postdosing with oxamyl technical. There was a significant increase ($p<0.05$) in the cholinesterase activity in males at 4 hours (↑5%). The differences at 2 and 4 hours in males were minor and/or an increase and therefore considered not to be of toxicological concern. Therefore, brain cholinesterase activity returned to normal levels by 2 hours postdosing in males and 3 hours postdosing in females. Brain cholinesterase activity was decreased ($p<0.05$) in male rats at 0.5 hours (↓46%), 2 hours (↓16%), and 3 hours (↓8%) postdosing and in female rats at 0.5 hours (↓39%), 2 hours (↓8%), and 3 hours (↓8) postdosing with methomyl technical. The differences at 2 hours in females and 3 hours in males and females were minor and considered not to be of toxicological concern. Therefore, brain cholinesterase activity returned to normal levels by 3 hours postdosing in males and 2 hours postdosing in females.

This cholinesterase inhibition reversibility study is classified **acceptable (nonguideline)** as it is not a required guideline study. It is acceptable for the purpose for which it was intended.

C. Study deficiencies - There were no deficiencies noted in the study.